REMARKS

Claims 40, 42, 44, 46, 56-58, and 61 are presently pending. The Examiner has maintained the obviousness rejections from the previous Office Action that are rebutted in the following order:

I. Rejections Under 35 USC §103(a)

A. Claims 40 and 61 are allegedly unpatentable over United States Patent No. 4,873,316 Meade et al., in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), Seegers et al. *Blood* 5:421-433 (1950), and further in view of van Cott and Velander *Expert Opinion on Investigational Drugs* 7:1683-1690 (1998), and previously cited Velander et al. *Proc. Natl. Acad. Sci. USA* 89:12003-12007 (1992)..

B. Claims 40, 42, 44, 46, 56 and 58 are allegedly unpatentable over United States Patent No. 4,873,316 Meade et al., in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), and further in view of Le Bonniec et al., *J Biochem* 266:137796-13803 (1991).

C. Claims 40 and 57 are allegedly unpatentable over United States Patent No. 4,873,316 Meade et al. in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), and further in view of Seegers et al., *Blood* 5:421-433 (1950); and further in view of Le Bonniec et al., *J Biochem* 266:137796-13803 (1991).

I. The Claims Are Not *Prima Facie* Obvious

Obviousness is currently determined based upon an evaluation of the magnitude of the differences between the claimed embodiment and the asserted prior art:

> In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966), the Court set out a framework for applying the statutory language of § 103 ... "Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained ...

KSR v. Teleflex, 127 S. Ct. 1727, 1734 (2007). Further, the *KSR* holding only cautioned against a strict application of the "teaching-suggestion-motivation test" such that an explicit teaching is not required to be found within the cited applications. Nonetheless, *KSR* has NOT changed the

law regarding the requirement to establish a *prima facie* case of obviousness by: i) finding *some motivation* to combine the references either explicitly or implicitly, ii) finding a teaching or suggestion of all the claim limitations in the cited references; and iii) demonstrating that the references provide sufficient technical detail such that one having ordinary skill in the art would be provided with a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A *Prima Facie* Case Of Obviousness.

A. Meade et al. And Jorgensen et al. Do Not Teach A Composition Of Completely Carboxylated Recombinant Prothrombin Polypeptide At A Concentration Of 0.5 MG/ML Derived From A Transgenic Mammal

The Applicants' note that the Examiner has provided three separate obviousness rejections. Notably, all the obviousness rejections depend upon an improper combination of Meade et al. and Jorgensen et al. The Applicants provide below rebuttal evidence showing that this improper combination of Meade et al. and Jorgensen et al. do not teach all the claimed elements and disclose inferior compositions, thereby rebutting the Examiner's alleged *prima facie* case of obviousness.

The Examiner states that Meade et al. discloses:

> ... an efficient means of producing large quantities of recombinant protein in the milk of transgenically altered mammals. A DNA sequence coding for a desired protein is operatively linked in an expression system to a milk-specific protein promoter or any promoter sequence specifically activated in mammary tissue ...

Office Action mailed June 2008, pg 4, that when placed in combination with Jorgensen et al. make the Applicants' claimed invention allegedly obvious. The Applicants disagree. A combination of Meade et al. and Jorgensen et al. would hardly result in an "efficient means" for transgenic protein expression/collection/isolation because the expressed protein concentrations are limited to micrograms/milliliter, much too low for commercial exploitation. The Applicants specifically pointed out that low yield compositions derived from *in vitro* culture methods (such as in Jorgensen et al.) are disadvantageous:

> Moreover, attempts to culture genetically altered cells to produce prothrombin polypeptides have produced uneconomically low yields and, generally, preparations of low specific activity.

Applicants' Specification pg 6 ln 5-7.

KSR has left untouched the requirement that a *prima faice* case of obviousness must provide evidence that all the claimed elements are disclosed in the asserted references. Such a showing of evidence is required under the *KSR* holding as the Court reinforced the need for a proper *Graham* analysis to support any obviousness rejection. In one aspect of a proper *Graham* analysis, the Examiner must identify and consider the differences between the cited art and the Applicants' claimed invention. In this case, the differences are significant, none of the asserted references teach the *in vivo* expression in milk of a recombinant prothrombin polypeptide at a concentration of 0.5 mg/ml (i.e., this is a missing element which immediately obviates a *prima facie* case of obviousness).

KSR requires an Examiner to provide an explicit analysis to support the obviousness rejection:

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents ... To facilitate review, this analysis should be made explicit. See *In re Kahn*, 441 F.3d 977, 988 (CA Fed. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness").

KSR v Teleflex, 127 S. Ct. 1727, 1740 (2007) [emphasis added]. This, the Examiner has not done. 'Articulated reasoning" requires a plausible discussion that, at a minimum, compares and contrasts the teachings of an asserted reference with the Applicants' specification. Merely pointing to single words, without the appropriate context, is wholly insufficient. As shown above, *KSR* cites *In re Kahn* to explain this requirement:

> ... mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole. [*In re Rouffet*, 149 F.3d] *at 1355, 1357.* ... to establish a prima facie case of obviousness ... the Board must articulate the basis ... In practice ... [t]his entails consideration of ... the "scope and content of the prior art" ...

In re Kahn 441 F.3d at 986 [emphasis added]. The Examiner's references are pointed to only for various isolated elements that can only be interpreted as the 'mere identification in the prior art of each element'.

Further, the Examiner has not identified explicit teachings within any of the asserted references such that a reasonable expectation of success is apparent. As a result of this lack of evidence of success in the asserted references, the Examiner has not met well settled patent law for establishing 'a reasonable expectation of success' such that the references explicitly predict that the recited claims would work:

> Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the method could be used to make proteins.

In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988)[emphasis added]. Recently, the Federal Circuit has reaffirmed *O'Farrell* in the wake of *KSR*:

> Specifically, this court observed that an obviousness finding was appropriate where the prior art "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and *evidence suggesting that it would be successful.*" 853 F.2d at 902 (emphasis added).

In re Kubin, 561 F.3d 1351, 90 U.S.P.Q.2D (BNA) 1417 (Federal Circuit 2009)[underlining in original, italics added]. Therefore, in order for an obviousness rejection to stand on 'a reasonable expectation of success', the cited references MUST provide some evidence of the expected success, NOT just mere speculation.

The Examiner has also not found all the Applicants' claimed elements to support the asserted reference combination. For example, the Examiner has already admitted that Meade et al. does not teach all the claimed elements:

> ... Meade et al. ... do[es] not indicate that recombinant prothrombin is made in milk.

Office Action mailed June 2008 pg. 4. The Applicants further submit that Meade et al. also does not teach the expression of any recombinant protein at levels of 0.5 mg/ml, much less prothrombin comprising a fully carboxylated Gla domain. To this point, Meade et al. only teaches an expression level that is one-thousand times lower than the Applicant's currently claimed embodiment:

> The G1 progeny produced 0.2-0.5 μg/ml of TPA in their milk.

Meade et al., col 7 ln 25-26 [emphasis added]. Jorgensen et al. cannot be properly combined with Meade et al., because Jorgensen et al. also does not teach a high expression level of completely carboxylated prothrombin:

> In the current study, recombinant prothrombin synthesized at levels of up to 0.55 μg/ml in Chinese hamster ovary cells is completely γ-carboxylated. When prothrombin expression levels are amplified 10-15-fold, however, only approximately 60% of the secreted prothrombin is sufficiently carboxylated *to bind to the conformation-specific antibodies*. Chinese hamster ovary cells are thus capable of more efficient γ-carboxylation of both prothrombin and Factor IX when expressed at low levels than when expression is amplified..

Jorgensen et al., pg 6733, lhc. The Examiner is reminded that Jorgensen's cell culture technique observed a 40% drop in carboxylated prothrombin at expression levels of 6.5 – 8.2 μg/ml (*infra*) when exposed to methotrexate concentrations that artificially increase expression rate. These levels are still one-hundred fold less than those disclosed by the Applicant's specification. Further, Jorgensen et al. identified this incompletely carboxylated prothrombin as "abnormal prothrombin":

> When prothrombin expression levels were amplified by subculturing transfected cells in the presence of 0.5 μg/ml of methotrexate, 6.5-8.2 μg/ml (1.3-1.6 $\mu g/10^6$ cells/24 h) of total prothrombin antigen was secreted. At these levels of prothrombin expression, native prothrombin concentrations were 4.2-4.4 μg/ml and abnormal prothrombin concentrations were 0.8-1.1 μg/ml.

Jorgensen et al. pg 6371 col 1. One having ordinary skill in the art would expect that if Jorgensen et al. were able to express prothrombin at 0.5 mg/ml (i.e., 500 μg/ml), the percentage of prothrombin that is "sufficiently carboxylated to bind to the conformation-specific antibodies" would be much less than 60%. As such, Jorgensen et al. does not provide any reasonable expectation of success, nor teach the Applicant's claimed element, that the disclosed plasmids are useful to produce completely carboxylated prothrombin at expression levels of at least 0.5 mg/ml.

Clearly, the Applicants' specification teaches superior expression of any recombinant protein into milk of a transgenic mammal relative to the teachings of Meade et al. and Jorgensen et al. As neither Meade et al. nor Jorgensen et al. teach an *in vivo* expression platform for expressing any recombinant protein at a concentration of 0.5 mg/ml, they cannot be combined to

teach the Applicant's Claim 40. The Applicant's have disclosed a superior and more advantageous composition than either Meade et al. or Jorgensen et al.:

> Yields of polypeptides of the invention in this regard in preferred embodiments are sufficiently high for recovery of useful amounts. In particularly preferred embodiments the yields are substantially better than those previously achieved by other methods, either as to concentration, total amount of polypeptide obtained, activity, specific activity or homogeneity, including homogeneity of activity, specific activity, physiological activity, general or specific post-translational modification, including but not limited to γ-carboxylation and glycosylation, or a combination of one or more of any of the foregoing, proteolytic processing and or activation, among others.

Applicants' Specification pg 35 ln 3-10. The Applicants submit that well settled case law holds that demonstrated superiority and advantages overcome obviousness:

> Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness.

In re Chupp, 816 F.2d 643, 646, 2USPQ2d 1437, 1439 (Fed. Cir. 1987), *See also, MPEP 716.02(a) II.* In affirming a non-obviousness District Court ruling, superior results has been supported in the context of *KSR* in recent rulings by the Federal Circuit:

> The *KSR* Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR, 127 S. Ct. at 1732.* In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." Id. That is not the case here.

In re Takeda, 492 F.3d 1350, 1358 (Fed. Cir 2007), and,

> Here, the court found that pioglitazone exhibited unexpectedly superior properties over the prior art compound b.

In re Takeda, 492 F.3d 1350, 1361 (Fed. Cir 2007).

Therefore, the Examiner's combination of Meade et al. and Jorgensen et al. fails to create a *prima facie* case of obviousness in regards to all of the Applicants' pending claims. The Examiner is respectfully requested to withdraw the pending rejection.

B. Velander et al. Is Of No Help

The Examiner states that:

> At the time of filing, Velander et al. teach that recombinant protein expressed in the milk of transgenic pigs can be expressed as high as 1000 μg/ml (Velander et al., page 12005, 1st col., parag. under "Protein Analysis", see also Figure 1).

Office Action pg 3. The Applicants' disagree because the Velander et al. reference explicitly explains that construct expression is highly unpredictable and must be determined empirically:

> Additionally, there is no direct correlation between the level of expression in transgenic mice compared to livestock for a given genetic construct (2, 4). For example, transgenic pigs expressed a 7.2-kbp genomic fragment of mouse whey acidic protein (WAP) at a 2- to 100-fold greater level (2, 5) than transgenic mice with the same construct. Therefore, the choice of employing a cDNA versus a genomic construct to synthesize a given protein in the mammary gland of livestock can become complex.

Velander et al., PNAS 89:12003-12007 1st col (Dec. 1992). The scope and context of Velander's teachings does not support the Examiner's assumption that just because a WAP promoter produced human protein C at 1 mg/ml, that it should be predictable that it would be expected to produce a fully carboxylated prothrombin at 0.5 mg/ml[1].

The Examiner is respectfully requested to withdraw the present rejection.

C. Seegers et al. Is Of No Help

The Examiner states that in regards to Claim 40 and 57:

> Seegers et al. teach that activation of purified prothrombin is accomplished by dissolving the purified prothrombin in a 25% solution of sodium citrate ...

Office Action pg 7. The Examiner has not shown that Seegers et al. remedies the deficiencies of Meade et al. and Jorgensen et al. by teaching a highly expressed fully carboxylated recombinant prothrombin. Consequently, the Applicants argue that Claim 40 is patentable, thereby mooting the rejections under Seeger et al. to dependent claims.

[1] The Examiner is reminded that - under the law - an Examiner is NOT one skilled in the art; mere opinion of the Examiner on what one skilled in the art might believe does not count. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) ("[T]he examiner's assumptions do not constitute the disclosure of the prior art.").

D. van Cott et al. Is Of No Help

The Examiner states that in regards to Claims 40 and 61:

> According to van Cott and Velander, while transgenic mice were poor at gamma-carboxylating recombinant proteins, transgenic pigs were able to gamma-carboxylate recombinant proteins excreted in milk up to 0.1 g/l/h [29, ...

Office Action pg 6. The Applicants submit that the Examiner has ignored the fact that van Cott et al. were not discussing the γ-carboxylation of prothrombin:

> ... the mouse mammary gland was a very poor γ-carboxylator of recombinant Protein C and FIX, while the pig was able to γ-carboxylate up to 0.1 g/l/h ...

van Cott et al., pg 1686 rhc – 1687 lhc [emphasis added]. Further, the cited passage references citation (29) that is the Examiner's cited Velander et al. As discussed above, Velander et al. does not teach the expression of prothrombin, and does not disclose any recombinant expression at a level of 0.5 mg/ml. Further, van Cott et al. does not even mention prothrombin as a possible protein for expression. van Cott et al. does not provide any evidence that Protein C and Factor IX were fully carboxylated, only that γ-carboxylation in pigs is better than in mice. Third, the prothrombin expression level now recited in Claim 40 is 5 times superior to that referred to in van Cott et al. (i.e., 0.1 g/l/h = 0.1 mg/ml/h). As explained above, these superior and advantageous results overcome the Examiner's obviousness argument.

The Applicants submit that van Cott et al. does not provide sufficient teachings, such that when combined with Meade et al. and Jorgensen et al., that one having ordinary skill in the art could make and use a transgenic mammal capable of secreting transgenic prothrombin in milk at a level of at least 0.5 mg/ml.

E. Le Bonniec et al. Is Of No Help

The Examiner states that:

> Le Bonniec et al. teach that prothrombin is activated by bovine factor Xa ... [and] that activation of prothrombin yields thrombin ...

Office Action pg 6. The Applicants argue that Le Bonniec et al. does not remedy the lack of a prima facie case of obviousness in view of the other asserted references discussed above. Specifically, Le Bonniec et al. does not provide any evidence teaching recombinant prothrombin in the milk of a transgenic mammal having a concentration of at least 0.5 mg/ml.

F. Conclusion

The Examiner has not provided any evidence showing that milk produced by a transgenic mammal can have at least 0.5 mg/ml of fully carboxylated recombinant prothrombin. As such, the Examiner has failed to put forth a *prima facie* case of obviousness. The Examiner is respectfully requested to withdraw all the pending rejections and pass the above claims to allowance.

CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 781-828-9870.

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